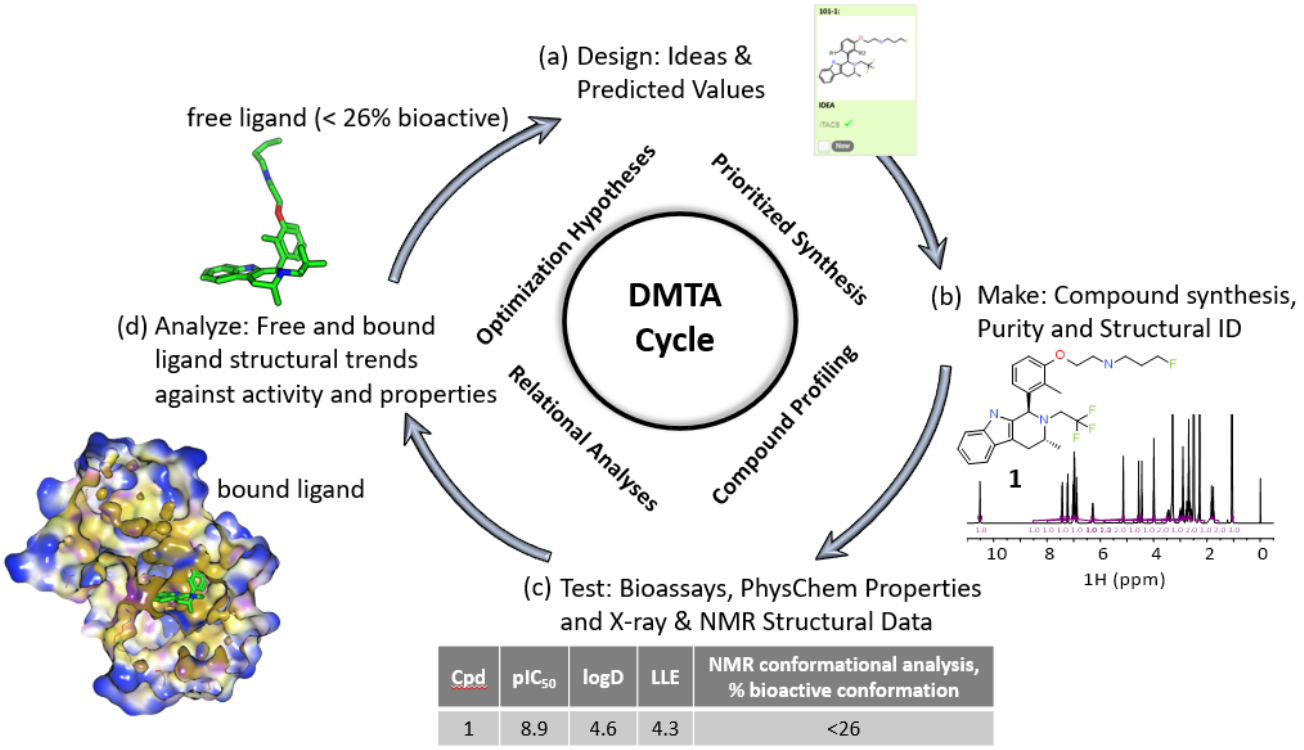
Dear Prof. Ferrage,

We are pleased with your decision to publish subject to corrections. Thank you for confirmation that the manuscript is within the scope of Magnetic Resonance.

We are also committed to Open Data. We are working with Chemotion repository for our ^{1}H NMR spectra. The data has been accepted and the pre-publication embargo has been released. The live DOI links have been added under to the NMR multiplet string in the manuscript for each compound (p.10, lines 233, 244, and 252).

We have simplified Figure 1. There are fewer fonts and colors. Extraneous details to the illustration have been moved to the caption or altogether. The four components of the design cycle have been labeled a-d, then explained in the figure caption.



Cpd	pIC$_{50}$	logD	LLE	NMR conformational analysis, % bioactive conformation
1	8.9	4.6	4.3	<26

Figure 1. An illustrative Medicinal Chemistry design – make – test – analyze (DMTA) cycle for drug discovery; the example shown is taken from a recent Oncology R&D project (Scott et al., 2016; Scott et al., 2019; Scott et al., 2020). (a) Design: Medicinal Chemists design drug molecule ideas, using predicted values from computational models to prioritize which virtual molecules to synthesize. (b) Make: Compounds are synthesized and NMR plays a key role for structural identification and analysis of compound purity. (c) Test: Compound profiling includes bioassays to quantify activity, such as target inhibition (pIC$_{50}$), and physico-chemical properties, such as the octanol/water partition coefficient (log*D*). X-ray structure of the bound ligand-protein complex and NMR free ligand conformations are measured, including relative population of the bioactive bound conformation. (Balazs et al., 2019). (d) Analyze: compound free and bound structures are analyzed against measured properties to rationalize structure activity and property relationships to derive new hypotheses for improved designs in step (a) of the cycle. Typical discovery projects comprise ~1000 cycles from hit to drug candidate.

In Figure 5, p.8 line 187, we added, “(dark dot in the center of the radial plots).” In addition, in Figure 3, when the radial plots are first described, we’ve added, for further clarity, to “The conformational space sampled during the simulation is reported either as a function of the simulation time (radial plots, from the center at the start and spiraling outward” the following text: p.5 lines 117-118, “, with dark dots indicating initial and last sampled dihedral angles) …” Similarly, to the methods section, page 11, line 269 after, “Radial plots show the evolution of the simulation time from the start, at the center”, we’ve included for clarity, “indicated by a dark dot, and radiating outward until the final sampled conformer, also indicated by a dark dot.”

Section 3.1, the title, “NMR spectroscopy” has been made more specific: ^{1}H 1D and 2D ROESY solution NMR Spectroscopy. In this section, p.9 line 225, Schleucher et al., 1995; Thiele et al., 2008, the two relevant EASY ROESY references were added in line and page 16, in the full references were added alphabetically.

Line 410, Schleucher, J., Quant, J., Glaser, S. J., Griesinger, C.: A Theorem Relating Cross-Relaxation and Hartmann-Hahn Transfer in Multiple-Pulse Sequences. Optimal Suppression of TOCSY Transfer in ROESY, J. Magn. Reson. A, 112, 144-151, https://doi.org/10.1006/jmra.1995.1025, 1995.

Line 435, Thiele, C., Petzold, K. and Schleucher, J.: EASY ROESY: Reliable Cross-Peak Integration in Adiabatic Symmetrized ROESY, Chem Eur J., 15, 585-588, https://doi.org/10.1002/chem.200802027, 2009.

The last changes were to expand acronyms at first use:

p.10, l.250, the acronym (EXSY) was added after exchange spectroscopy, as EXSY is used on p.13 line 314 in the acknowledgements sections.

p. 11 l.274, SMARTS was expanded prior to the use of the acronym.

p.11 l.280, GIAO DFT

p.12 l.287 GUI was replaced by graphical user interface in the text.

p.12 l.297 proteolysis targeting chimeras (PROTACs)

We thank you for this excellent opportunity to participate with a celebratory contribution to Geoffrey Bodenhausen's Festschrift.

On behalf of all the authors,

Amber Balazs